# Atopic conditions other than asthma and risk of the 2009 novel H1N1 infection in children: A case–control study

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## ABSTRACT

*A recent study showed an increased risk of 2009 novel H1N1 influenza (H1N1) infection among asthmatic children. Little is known whether this is true for other atopic conditions. This study was designed to determine the association between atopic dermatitis and/or allergic rhinitis and the risk of H1N1 infection among children. We conducted a case–control study in Olmsted County, MN. We randomly selected children ≤18 years of age with a positive test for H1N1. Controls were randomly selected from a pool of residents with negative H1N1 tests and were matched to cases with regard to birthday, gender, clinic registration date, diagnostic test, and month of influenza testing using frequency matching. We compared the frequency of atopic conditions other than asthma between cases and their matched controls. We enrolled 168 cases and 172 controls. Among cases, 91 (54.2%) were male patients, and 106 (63.1%) were white. The median age of cases was 6.3 years (interquartile range, 3.1–11.5). Among cases, 79 (47.0%) had atopic dermatitis and/or allergic rhinitis diagnosed before or after the index date, whereas 54 (31.4%) controls had such conditions (odds ratio [OR], 1.89; 95% CI, 1.15–3.12; p = 0.012, adjusting for asthma status, 2008–2009 seasonal influenza vaccine, time of illness at index date, and other comorbid conditions). History of receiving 2008–2009 seasonal influenza vaccine was associated with H1N1 infection (adjusted OR, 2.06; 95% CI, 1.32–3.28; p = 0.002). Our results suggest an association between H1N1 infection and atopic conditions other than asthma. The association between 2008–2009 seasonal influenza vaccinations and the risk of H1N1 requires further investigation.*

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The first reported cases of 2009 H1N1 influenza in the United States occurred in April 2009. Within a few months after its outbreak, it became pandemic. As of July 2010, the World Health Organization reported >214 countries were affected by H1N1, and >18,000 deaths worldwide.[1] Among the individuals affected by H1N1, children had the highest rates of emergency room visits and hospitalization rates. A few reports from different countries identified asthma as the single most common chronic condition among hospitalized or deceased individuals with H1N1.[2–5]

The literature suggests that individuals with asthma and other atopic conditions have suboptimal innate and adaptive immune functions against microbial agents.[6–11] Indeed, individuals with atopic conditions have been reported to have higher risks of microbial infections than those without such conditions.[12–18] A recent study showed that the incidence of H1N1 infection was higher in children with asthma than in children without asthma (odds ratio [OR], 4; 95% CI, 1.8–9; $p < 0.001$),[19] suggesting asthma might be associated with an increased risk of H1N1 infection. At present, it is unknown whether this is true for other atopic conditions such as atopic dermatitis or allergic rhinitis.

We hypothesized that children with allergic rhinitis and/or atopic dermatitis have a higher risk of H1N1 infection than those without such conditions. To test this hypothesis, we conducted a case–control study, comparing the frequency of atopic dermatitis and/or allergic rhinitis between children with and without H1N1.

## METHODS

The Institutional Review Boards at both the Mayo Clinic and Olmsted Medical Center approved this study.

### Study Design

This was a retrospective case–control study, which enrolled pediatric H1N1 cases based on a positive reverse transcription polymerase chain reaction or rapid antigen tests for influenza A, and matched controls from the same virology databases. The frequency of physician diagnosis of atopic dermatitis and/or aller-

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gic rhinitis before or after the index date of H1N1 was then compared between the cases and their matched controls. The study period was from June 1, 2009, to November 30, 2009, at the time of the second wave of the 2009 H1N1 influenza pandemic.[20] During this time, the Center for Disease Control and Prevention reported that almost all (98%) positive influenza A cases were caused by H1N1.[21]

We used an incidence-density case–control approach with 1-to-1 matching, which identifies controls at the time of cases, so controls were at risk of becoming cases. The main advantage of this approach is that the estimated OR approximated to the relative risk. Additionally, it was not required to assume a low incidence of the disease of interest.[22] Controls were matched to cases using frequency matching, in which the overall frequency of the matched characteristics is similar between cases and controls.[23]

### Study Setting

Study subjects were children who resided in Olmsted County, located in southeast Minnesota. The population of Olmsted County has a demographic distribution similar to the upper Midwest of the United States.[24] Olmsted County has unique epidemiological advantages for retrospective case–control studies. The health care environment is self-contained (two medical centers provide medical care to >95% of the residents). In addition, medical records of all residents of Olmsted County, who have given written authorization for themselves or their children, are linked and available for approved medical research under the auspices of the Rochester Epidemiology Project, which has been continuously funded for 40 years by the National Institutes of Health.[24]

### Study Population

*Eligibility Criteria.* Children ≤18 years of age who resided in Olmsted County, MN, at the time of index date of H1N1 and whose parents granted research authorization for using medical records were eligible. Participants were required to have been tested for influenza A from a respiratory source either by a real-time reverse transcription polymerase chain reaction or by a commercial influenza rapid antigen diagnostic test. The participants and their H1N1 test results were listed in the virology databases from Mayo Clinic and Olmsted Medical Center that contained all individuals tested for influenza in Olmsted County during the study period. To ensure community exposure for H1N1, individuals had to have an H1N1 test date at least 2 days after any hospitalization. If an individual was tested for influenza after being admitted to the hospital, the test date must have been within 2 days of admission. If an individual was discharged from the hospital without influenza-like symptoms and then readmitted, there had to be at least 2 days between hospitalizations.

*Exclusion Criteria.* Subjects were excluded if (1) they were not residents of Olmsted County at the time of the test for influenza, (2) there was no authorization for using medical records for research, or (3) there was insufficient information in medical records to determine exposure status.

*Identification of Cases and Controls.* Case Ascertainment. Cases were randomly selected from the virology databases. Cases of H1N1 were defined as having a positive test for influenza A during the study period. We selected an age-stratified random sample of incident cases of H1N1 from the list of all children who had a positive H1N1 test to ensure representation of all age groups. We considered the date of the first positive influenza A test as the index date of H1N1.

Identification of Controls. A random sample of controls having a negative test for influenza A from each institution was selected from the databases. The matching criteria include gender, birthday (within 6 months for patients <18 years and within 1 year for patients 18 years of age), and H1N1 index date within 1 month. To ensure similar follow-up time between cases and controls to ascertain the exposure (*i.e.*, atopic conditions), controls were also matched to cases by clinic registration date within 1 year.

*Ascertainment of Exposure Status (*i.e.*, Atopic Dermatitis and Allergic Rhinitis).* We conducted a comprehensive medical record review to determine the atopic status of the study subjects. Atopic dermatitis was determined based on a physician diagnosis of atopic dermatitis or eczema documented in medical records before or after the index date of H1N1 infection. Similarly, allergic rhinitis was ascertained by a physician diagnosis of allergic rhinitis or hay fever documented in medical records. We have previously used this ascertainment method for atopic conditions.[15,17] To determine temporal relationship between exposure status (atopic conditions) and outcome (H1N1 infection), we recorded the incidence dates of each atopic condition (*i.e.*, the earliest date of a physician diagnosis documented in medical records).

*Other Variables.* Additional data elements were also extracted from the medical records including sociodemographic variables, duration of illness associated with the H1N1 test; history of contacts with influenza-like illness, other comorbid conditions, H1N1, and 2008–2009 seasonal influenza immunization status; medication usage including oseltamivir; and asthma

Table 1 **Association between risk of H1N1 infection and history of atopic conditions other than asthma after adjusting for covariates**

| | Controls ($n$ = 172) | Cases ($n$ = 168) | Unadjusted OR (95% CI), $p$ Value | Adjusted OR* (95% CI), $p$ Value |
|---|---|---|---|---|
| History of atopic dermatitis and/or allergic rhinitis ever,# $n$ (%) | | | | |
| No | 118 (68.6) | 89 (53.0) | Referent | Referent |
| Yes | 54 (31.4) | 79 (47.0) | 1.93 (1.24–3.02), 0.003 | 1.89 (1.15–3.12), 0.012 |
| History of atopic dermatitis and/or allergic rhinitis before H1N1 index date, $n$ (%) | | | | |
| No | 118 (68.6) | 96 (57.1) | Referent | Referent |
| Yes | 54 (31.4) | 72 (42.9) | 1.63 (1.05–2.55), 0.029 | 1.55 (0.93–2.59), 0.091 |

**Adjusted variables included asthma status at H1N1 index date 2008–2009 seasonal influenza vaccine, time of illness at H1N1 index date, and history of one or more comorbid conditions other than asthma.*
*#Prevalence of atopic dermatitis and/or allergic rhinitis before or after index date of H1N1 influenza.*
*OR = odds ratio.*

status. Influenza immunization status was determined using medical records. Asthma status was based on predetermined criteria extensively used in epidemiological research and found highly reliable.[25–36]

### Data Analysis

Data were summarized with descriptive statistics, including counts and percentages for categorical variables or medians for continuous variables. We characterized the study subjects and assessed similarity between cases and their corresponding controls. We conducted univariate analyses to identify all pertinent covariates and confounders. For categorical variables, the two-sample chi-square test was used to compare the distribution of a variable of interest between cases and controls. For discrete or continuous variables, we used the Wilcoxon rank sum test for comparison of the medians. Data were fit to logistic regression models to estimate ORs and their corresponding 95% CI based on unmatched analysis. All statistical significance was tested at a two-sided $\alpha$-error of 0.05. We estimated that a sample size of 170 cases with their corresponding matched controls offered 80% statistical power to detect an OR of 2.5, assuming a 10% prevalence of asthma and other atopic conditions in the control group.[13,15] All analyses were performed with the JMP statistical software package (Version 9.0.1; SAS Institute, Inc., Cary, NC).

## RESULTS

### Study Subjects

A total of 453 children who were residents of Olmsted County had a positive H1N1 test during the study period. We randomly selected 174 cases with 172 frequency-matched controls. Of the 174 cases, 168 were eligible and 6 were excluded (1 subject was not resident of Olmsted County, 2 did not provide research authorization, and 3 did not have sufficient information in medical records for the study). The characteristics of the study subjects are summarized in Table 1. More than 95% of the study subjects did not receive the H1N1 vaccine before the index date. Only three cases (1.8%) and none of the controls received oseltamivir before the index date. The median duration of illness for cases and controls was 3 days. No controls became cases during the study period.

### The Association between Atopic Dermatitis/Allergic Rhinitis and H1N1 Infection

The association between atopic dermatitis/allergic rhinitis and H1N1 infection is summarized in Tables 1 and 2. Among cases, 72 (42.9%) had atopic dermatitis and/or allergic rhinitis diagnosed before the index date; whereas among controls, 54 (31.4%) had such conditions (OR, 1.63; 95% CI, 1.05–2.55; $p$ = 0.029). Among cases, 79 (47.0%) had atopic dermatitis and/or allergic rhinitis diagnosed before or after the index date; whereas among the controls, 54 subjects (31.4%) had such conditions (OR, 1.93; 95% CI, 1.25–3.02; $p$ = 0.003). Asthma was not associated with risk of H1N1 infection. In the multivariate model, the association between atopic conditions other than asthma diagnosed before or after the index date and H1N1 infection remained significant after adjusting for asthma status at H1N1 index date, history of 2008–2009 sea-

Table 2 **Sociodemographic and clinical characteristics of patients with H1N1 infection and their matched control subjects**

| | Controls ($n$ = 172) | Cases ($n$ = 168) | OR (95% CI), $p$ Value |
|---|---|---|---|
| Age at case's index date (yr) | | | |
| Median (IQR)§ | 6.2 (1.9–14.0) | 6.3 (3.1–11.5) | — |
| Gender, $n$ (%) | | | |
| Male | 94 (54.7) | 91 (54.2) | — |
| Female | 78 (45.3) | 77 (45.8) | — |
| Diagnostic method for influenza, $n$ (%) | | | |
| Polymerase chain reaction | 155 (90.1) | 150 (89.29) | — |
| Antigen rapid test | 17 (9.9) | 18 (10.7) | — |
| Ethnicity, $n$ (%) | | | See results below |
| Hispanic/Latino | 6 (3.5) | 3 (1.8) | |
| American Indian/Alaska Native | 0 (0.0) | 0 (0.0) | |
| Asian | 10 (5.8) | 13 (7.7) | |
| Hawaiian/Pacific Islander | 0 (0.0) | 0 (0.0) | |
| Black/African American | 17 (9.9) | 23 (13.7) | |
| White | 113 (65.7) | 106 (63.1) | |
| Unknown | 26 (15.1) | 23 (13.7) | |
| White | 113 (65.7) | 106 (63.1) | Referent |
| Nonwhite | 33 (19.2) | 39 (23.2) | 1.26 (0.74–2.14), 0.396 |
| Unknown | 26 (15.1) | 23 (13.7) | 0.94 (0.51–1.75), 0.853 |
| Duration of symptoms by H1N1 index date, $n$ (%) | | | |
| ≤2 days | 91 (52.9) | 109 (64.9) | Referent |
| ≥3 days | 59 (34.3) | 44 (26.2) | 0.62 (0.39–1.01), 0.052 |
| Unknown | 22 (12.8) | 15 (8.9) | 0.57 (0.28–1.16), 0.118 |
| History of fever and cough, $n$ (%) | | | |
| No | 74 (43.0) | 29 (17.3) | Referent |
| Yes | 98 (57.0) | 139 (82.7) | 3.62 (2.19–5.97), <0.001 |
| History of contact with a person with Influenza-like illness within a week before H1N1 index date | | | |
| No | 111 (64.5) | 96 (57.1) | Referent |
| Yes | 61 (35.5) | 72 (42.9) | 1.36 (0.88–2.11), 0.163 |
| Comorbidities other than asthma before index date,* $n$ (%) | | | See results below |
| Hemoglobinopathies | 2 (1.2) | 2 (1.2) | |
| Cardiopulmonary | 6 (3.5) | 5 (3.0) | |
| Neurodevelopmental | 13 (7.6) | 19 (11.3) | |
| Chronic renal diseases | 0 (0.0) | 1 (0.6) | |
| Immunosuppression/autoimmune | 4 (2.3) | 4 (2.4) | |
| Endocrine/metabolic | 1 (0.6) | 2 (1.2) | |
| None | 149 (86.6) | 138 (82.1) | Referent |
| One or more comorbid conditions | 23 (13.4) | 30 (17.8) | 1.41 (0.78–2.54), 0.254 |
| History of receiving 2008–2009 seasonal influenza vaccine, $n$ (%) | | | |
| No | 96 (55.8) | 61 (36.3) | Referent |
| Yes | 76 (44.2) | 107 (63.7) | 2.22 (1.43–3.42), <0.001 |

Table 2 **Continued**

| | Controls ($n$ = 172) | Cases ($n$ = 168) | OR (95% CI), $p$ Value |
|---|---|---|---|
| History of receiving H1N1 influenza vaccine before H1N1 index date, *n* (%) | | | |
| No | 165 (95.9) | 163 (97.0) | Referent |
| Yes | 7 (4.1) | 5 (3.0) | 0.72 (0.23–2.33), 0.585 |
| History of asthma before H1N1 index date, *n* (%) | | | |
| No | 116 (67.4) | 105 (62.5) | Referent |
| Yes | 56 (32.6) | 63 (37.6) | 1.24 (0.80–1.94), 0.340 |
| History of atopic conditions before index date, *n* (%) | | | |
| Allergic rhinitis only | 24 (13.9) | 32 (19.1) | 1.45 (0.81–2.59), 0.206 |
| Atopic dermatitis only | 17 (9.9) | 27 (16.1) | 1.75 (0.91–3.34), 0.089 |
| Atopic dermatitis and allergic rhinitis | 13 (7.6) | 13 (7.7) | 1.03 (0.46–2.28), 0.950 |
| Atopic dermatitis and/or allergic rhinitis | 54 (31.4) | 72 (42.9) | 1.63 (1.05–2.55), 0.029 |
| History of atopic conditions ever,# *n* (%) | | | |
| Allergic rhinitis only | 24 (13.9) | 32 (19.1) | 1.45 (0.81–2.59), 0.206 |
| Atopic dermatitis only | 16 (9.3) | 30 (17.9) | 2.12 (1.11–4.05), 0.021 |
| Atopic dermatitis and allergic rhinitis | 14 (8.1) | 17 (10.1) | 1.27 (0.61–2.67), 0.526 |
| Atopic dermatitis and/or allergic rhinitis | 54 (31.4) | 79 (47.2) | 1.93 (1.25–3.02), 0.003 |

**Comorbid conditions were not mutually exclusive because subjects could have more than one condition.*
*#Prevalence of atopic dermatitis and/or allergic rhinitis before or after index date of H1N1 influenza.*
*§Wilcoxon rank sum test was used to compare medians.*
*OR = odds ratio; IQR = interquartile range.*

sonal influenza vaccine, time of illness at H1N1 index date, and history of one or more comorbid conditions other than asthma (adjusted OR, 1.89; 95% CI, 1.15–3.12; $p$ = 0.012).

### Other Variables and H1N1

Comorbid condition was not associated with risk of H1N1 infection (OR, 1.41; 95% CI, 0.78–2.54; $p$ = 0.254). There were no differences in the proportions of contacts with influenza-like illness between cases and controls (OR, 1.36; 95% CI, 0.88–2.11; $p$ = 0.163). Patients who had received the 2008–2009 seasonal influenza vaccine were more likely to be cases than controls (adjusted OR, 2.06, 95% CI, 1.32–3.28; $p$ = 0.002).

## DISCUSSION

Our results showed an association between symptomatic H1N1 infection and atopic conditions other than asthma. Our results are unlikely to be confounded by the H1N1 vaccine effect, because >95% of the study subjects did not receive this vaccine. An important concern in interpreting our results is detection bias, which arises from different medical care–seeking behavior or different H1N1 ascertainment methods between children with and without atopic conditions (*e.g.*, individuals with atopic conditions may seek health care more rapidly or more frequently than individuals without such conditions). To address this concern, our controls were selected from subjects who had undergone testing for influenza at the same time as cases, and they were also matched by diagnostic method.

There are no previous studies to compare our results. Atopic conditions other than asthma are associated with an increased risk of viral and bacterial infections.[15,17,37] A recent prospective study showed children with asthma were more likely to develop H1N1 infection than nonasthmatic children.[19] In our study the main reason for the lack of the association between asthma and risk of H1N1 infection is probably because of overrepresentation of asthma in the control group and a trend toward delayed testing for H1N1 infection in asthmatic patients. Given the greater likelihood of detecting influenza virus during days 2 through 6 of illness, we examined the proportion of asthmatic patients (cases and controls) tested outside of this window. There were no differences in the proportion of children with and without asthma among cases who were tested during the periods of <2 or >6 days of

illness (53% versus 46%; $p = 0.67$). Among controls, the corresponding percentages were 60 and 46%, respectively ($p = 0.096$). Children with a diagnosis of asthma might delay evaluation for H1N1 infection after trial of asthma medications for nonspecific upper respiratory symptoms of H1N1, which might miss the window of detection by test. Although there was no statistically significant difference in the duration of illness between cases and controls, cases appeared to have a shorter duration of illness but were more symptomatic with influenza. We postulate that H1N1 cases with more influenza symptoms were likely to seek more prompt medical evaluation and treatment, which might result in a relatively shorter duration of illness. However, because controls were identified from individuals who had sought medical evaluation and test for H1N1, it is unlikely to affect the interpretation of our study results.

The underlying mechanisms for the increased risk of H1N1 infection in children with atopic conditions other than asthma remain to be determined. Previous studies showed deficiency of β-defensin and cathelicidin in patients with atopic dermatitis suggesting innate immune defects among patients with atopic conditions and increased susceptibility to viral infections.[38,39] Recent studies suggest that mutations in the filaggrin gene are associated with an increased risk of atopic dermatitis, leading to a heritable epithelial barrier defect and diminished epidermal defense mechanisms against microbial organisms,[40–44] but the mutations increase risk of allergic rhinitis and asthma only in the context of eczema.[43] Filaggrin expression has not been detected in human bronchial epithelial cells but in the anterior vestibulum of the nose.[43] Based on our study findings on the increased risk of H1N1 influenza among patients with atopic dermatitis, filaggrin mutations in the nasal epithelial cells might have an important implication on susceptibility to viral infections. Given the reported increased risk of H1N1 in children with asthma,[19] additional studies are needed to understand the mechanisms underlying the increased risk of H1N1 influenza in the context of the unique alteration in immune functions and airway architecture in atopic individuals.

Children who had received the 2008–2009 seasonal influenza vaccine were more likely to develop H1N1 infection (adjusted OR, 2.04, 95% CI, 1.30–3.20; $p = 0.002$). Indeed, a previous study showed an increased risk of H1N1 infection in recipients of the 2008–2009 seasonal influenza vaccine.[45] Although, the underlying mechanisms of this association remain unknown, the hypothesis of a broad nonspecific immunity that develops shortly after influenza infection was postulated.[46,47] According to this hypothesis, children who had received the 2008–2009 influenza vaccine were less likely to develop influenza infection during the previous season to the pandemic, which, in turn, led to an increased risk of H1N1. Additional studies using animal models are needed to test this hypothesis. Alternatively, previous seasonal influenza might be a surrogate marker for clinical conditions with increased risk of influenza infection and thus, parents of children with these conditions might be more likely to get their children receive seasonal influenza vaccines, which might not necessarily mitigate the risk of H1N1 influenza.

The main strengths of our study are the epidemiological advantages, including the self-contained health care environment and the linkage of medical records. Cases and controls were directly identified from the same sampling frame, minimizing selection bias. We selected incident cases of H1N1 and controls from the list of patients tested for H1N1, minimizing detection bias stemming from exposure status (atopic conditions). Finally, this study addressed the effect of a new influenza strain in a population of children immunologically naive to the infecting strain.

Our study has inherent limitations because of its retrospective design. The detection of atopic dermatitis and allergic rhinitis was based on medical record review. This limitation, however, is subject to a nondifferential misclassification bias, which is likely to support the null hypothesis. Our data abstractors were not blinded, which could introduce performance bias. However, the ascertainment of atopic conditions were clearly specified, which should minimize this bias.[36] We included only subjects who sought medical care and were tested for influenza, potentially limiting the external validity of our results (minimizing detection bias).

In conclusion, atopic conditions other than asthma were associated with the risk of H1N1 infection in children. Children with such conditions may be an unrecognized high-risk group for influenza. If our results are replicated, public health agencies may consider including children with atopic dermatitis and/or allergic rhinitis in a high-risk group for the influenza vaccine policy. The association between a history of seasonal influenza vaccinations and the risk of H1N1 requires further investigation.

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## Erratum

In the article *Pharmacotherapeutic strategies for allergic rhinitis: Matching treatment to symptoms, disease progression, and associate conditions* Allergy Asthma Proc 34:301–311, 2013; doi: 10.2500/aap.2013.34.3676, on page 306, under the heading INSs and Intranasal Antihistamines, the second sentence is incorrect: In a 14-day, randomized, double-blind study, 610 patients with moderate-to-severe nasal SAR symptoms received either monotherapy with azelastine or fluticasone nasal spray, both sprays, or placebo.[47]
In that trial, both sprays were not used for therapy. Fluticasone plus azelastine was administered in a single spray and single delivery device as part of the MP29–02 (Dymista) clinical trial registration program.

The author regrets the error.

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